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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,864	11/24/2000	David Scheinberg	D6126	4077

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EXAMINER

DAVIS, MINH TAM B

ART UNIT PAPER NUMBER

1642

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/721,864	Applicant(s) SCHEINBERG ET AL	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 7 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 7 are being examined.

It is noted that the 103 rejection was withdrawn, in view of the amendment, but could be reinstated if the present 112, first paragraph issue were removed.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for sequentially reducing the size of a solid cancer greater than 1 mm in size, does not reasonably provide enablement for a method for sequentially reducing the size of a solid cancer greater than 1 mm in size, "such that the tumor growth probability approaches one". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant amends the claims such that now claims 1, 7 read on a method for increasing the probability of remission of solid cancerous tumor greater than 1 mm in size, by repeating killing additional layer of tumor cells, such that the **tumor growth**

probability approaches one, wherein the dose of the administered Bi-213-antibody is from about 0.1 mg/m^2 to about 10 mg/m^2 .

The response asserts that the requirement is not that every tumor cell must express antigen. The response asserts that a minimum of two atoms of Bi-213, delivering at least one alpha particle to each tumor cell, having an antibody bound, is demonstrably sufficient to destroy at least one layer of tumor cells in the spheroid model. The response concludes that even with the heterogeneous nature of tumor cells, with a suitable dose of Bi-213 antibody binding a sufficient number of antigen binding sites to repeatedly and sequentially kill tumor cells exposed on the outlayer of the solid tumor, the probability of remission would increase.

The response has been considered but is not found to be persuasive for the following reasons.

The specification calculates that to achieve a 5-year disease-free survival, the probability of killing all tumor cells must approach one (p.19). The specification calculates that 99% of patients would achieve a 5-year disease-free survival, if treatment potency was such that 10^7 tumor cells could be reduced to **1 single** tumor cell (emphasis added) (p.19, lines 18-21, bridging p. 20). The specification calculates that for 10^5 tumor cells, the probability is only 0.37, if one single cell remains.

In other words, for 10^5 cancer cells, to approach the probability of one, not even a single cancer cell remains or escapes from the treatment. For 10^7 cancer cells, to approach the probability of one, only a single cancer cell remains after treatment.

Further, the specification discloses that in Example 11, using a spheroid model of layers of cells from the same cell line, a single dose of the Bi-213 antibody conjugate eliminates 5 to 6 layers of cells, leaving behind a previously unexposed core of cells (p.39). The specification further discloses in Example 13, on pages 44-45, that under four daily doses of B-213-antibody conjugate, the tumor-free survival time for the LNCaP xenografted mice is 33 or 54 days (p.44). The specification discloses that one of the minimum requirement to achieve reliable cell killing depends on the number of receptor targets on the target cell (p.15). The specification further hypothesizes that since there are 10,000 possible sites per cell in leukemia, then 2 atoms will reach the cell and over 3 hours one will decay with an alpha into the cell and one, away from the cell, on average, and thus the minimum specific activity of about 10 mCi/mg is necessary (p.16).

It is noted that the same cell types, from the same cell line, are used in the spheroid model, which would not represent solid cancers in nature, which are expected to be heterogeneous, and containing cells that express tumor antigens at different levels even from a single tumor, in view of the teaching of Greiner et al, Hager et al, Kmshead et al, all of record.

One cannot predict that the claimed method would achieve the probability of tumor growth approaching one for the following reasons:

For 10^5 tumor cells, to approach the probability of one, not even a single tumor cell remains or escapes from the treatment. For 10^7 tumor cells, to approach the probability of one, only a single tumor cell remains after treatment. However, due to cancer heterogeneity, as taught by Greiner et al, Hager et al, Kemshead et al, all of record, one cannot predict whether every single cancer cell, especially from a large solid tumor would escape from being killed by the claimed antibody conjugate, nor how many cancer cells actually could escape from being killed

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by the claimed conjugate, because one cannot predict whether every single target cancer cell would have adequate amount of antigen on cell surface, such that an adequate amount of alpha particle from the claimed antibody conjugate could be delivered into the target cell to effectively kill the target cell, nor the number of cancer cells, that would have adequate amount of antigen on cell surface. In view of such unpredictability of the number or level of antigens of each individual cancer cell, due to the well known antigen heterogeneity, supra, and in view that one of the minimum requirements to achieve reliable cell killing depends on the number of receptor targets on the target cell, as clearly stated by Applicant in the specification, one cannot predict that the claimed method would kill all or all but one single cancer cell, for example, in patients having 10^5 or 10^7 tumor cells.

Further, the examples in the specification however are not commensurate with the scope of the claims. In Example 11, the spheroid model is not representative of solid cancers in nature, because the model is composed of the same cell types from the same cell line, supra. In Example 13, the results only indicate prolonging of cancer-free survival time. In Example 13, the median tumor-free survival time for treated mice is improved only to 33 or 54 days, as compared to 31 days of the control. In other words, in view that cancer death does occur after 33 or 54 days after treatment, the results clearly indicate that not all of the cancer cells are eradicated, thus resulting in cancer death of treated mice after 33 or 54 days. Further, the specification does not disclose how to detect a single or a few escaped cells, to achieve the tumor growth probability approaching one, especially in view that one cannot predict where in the body the escaped cancer cell is, after the cell is dislodged from the solid cancer mass by the treatment.

New Rejection Based on the Amendment

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 7 are indefinite for the use of the language “the tumor growth probability approaches one” in claim 1. It is not clear what “the tumor growth probability approaches one” means, in view that there is no definition of “the tumor growth probability approaches one”.

Conclusions

No claims are allowed.

The closest prior art is Simonson et al, 1990, of record, which teaches reduction of tumor mass by Bi-212 antibody (see 103 rejection in the Office action of 10/21/2004). The art, however, does not teach that the tumor growth probability approaches one.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.


JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
October 19, 2006